2016 update of the Portuguese recommendations for the use of biological therapies in children and adolescents with Juvenile Idiopathic Arthritis

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ABSTRACT

Objective: To provide evidence-based guidance for the rational and safe prescription of biological therapies in children and adolescents with juvenile idiopathic arthritis (JIAs), considering the latest available evidence and the new licensed biologics.

Methods: Rheumatologists and Pediatricians with expertise in Pediatric Rheumatology updated the recommendations endorsed by the Portuguese Society of Rheumatology and the Portuguese Society of Pediatrics based on published evidence and expert opinion. The level of agreement with final propositions was voted using an online survey.

Results: In total, 20 recommendations to guide the use of biological therapy in children and adolescents with JIAs are issued, comprising 4 general principles and 16 specific recommendations. A consensus was achieved regarding the eligibility and response criteria, maintenance of biological therapy, and procedures in case of non-response, for each JIA category. Specific recommendations concerning safety procedures were also updated.

Conclusions: These recommendations take into account the specificities of each JIA category and are intended to continuously improve the management of JIA patients.

Keywords: Recommendations; Juvenile idiopathic arthritis; Biological agents.

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INTRODUCTION

Juvenile Idiopathic Arthritis (JIAs) incorporates a heterogeneous group of arthritis of unknown etiology, beginning before the age of 16 and persisting for at least 6 weeks[1]. The International League of Associations for Rheumatology (ILAR) classifies childhood arthritis into 7 mutually exclusive categories: systemic arthritis (sJIA), oligoarthritis (oJIA), polyarthritis (pJIA) rheumatoid factor (RF) positive, pJIA RF negative, enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (jPsA) and undifferentiated arthritis. Beyond the first 6 months oJIA can be further classified as persistent oJIA, if still less than 5 joints are involved, or extended oligoarticular (eoJIA), if involvement of ≥5 joints occurs. In the case of sJIA, systemic features may persist or the disease may evolve into polyarthritis.

When conventional therapies fail to achieve disease control, biological agents proved to be effective in reducing JIA inflammatory burden[2].

In 2007, the Portuguese Society of Rheumatology published national recommendations for the use of biologics in JIA, aiming to optimize the management of children and adolescents with JIAs[3]. The recommendations were revised in 2011 and covered eligibility, monitoring, switching and safety procedures before and while on biological therapy[4]. Based on the progresses in this field and the new licensed biologics, the recommendations are now updated.

METHODS

The recommendations were elaborated by the Pediatric Rheumatology Working Group of the Portuguese Society of Rheumatology and the Rheumatology Section of the Portuguese Society of Pediatrics. A steering group constituted by Rheumatologists and Pediatricians with expertise in the management of JIA patients, defined the relevant questions and a literature search was performed, through November 2015, using primarily MEDLINE. The retrieved evidence was discussed and a set of new recommendations was drafted. All propositions were extensively debated and final recommendations formulated. The level of agreement was voted online, using a 1–10 scale with a vote of 1 meaning total disagreement and 10 meaning full agreement with the recommendation. A draft proposal of the final manuscript was afterwards presented for detailed review and final wording.

RESULTS

In line with the 2011 recommendations we present the general principles and then the guidance for starting, maintaining and stopping biologics (Table I). More emphasis is now placed on the treatment of each JIA category and on newly approved drugs or new indications. Off-label prescription is also addressed.

GENERAL PRINCIPLES

1. Rheumatologists and Pediatricians with experience in pediatric rheumatology are the specialists who should care for JIA patients

An experienced pediatric rheumatology team provides the best care for children with arthritis[5]. Biologics should only be prescribed in specialized clinics run by rheumatologists and/or pediatricians with documented expertise in pediatric rheumatology.

2. The treatment goal is to achieve normal function, quality of life and social participation, through tight disease control. JIA activity must be regularly monitored using valid instruments and should be used to guide appropriate treatment adjustments

The rate of active JIA progressing into adulthood is still high, as it is the risk for serious and lifelong complications[6,7]. Furthermore, approximately 12% to 38% of JIA patients will develop uveitis[8,9] and 50% to 75% of

TABLE I. RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPY IN JUVENILE IDIOPATHIC ARTHRITIS

General principles	Level evidence	Agreement Mean(SD)
1 Rheumatologists and Pediatricians with experience in pediatric rheumatology are the specialists who should care for JIA patients		9.6 (1.2)
2 The treatment goal is to achieve normal function, quality of life and social participation, through tight disease control. JIA activity must be regularly monitored using valid instruments and should be used to guide appropriate treatment adjustments		9.8 (0.5)
3 A definitive diagnosis of JIA and sustained articular, systemic or ocular inflammation are required when starting a biologic		9.5 (0.7)
4 The biologic choice must take into account the JIA phenotype		9.6 (0.7)
Biological therapy for polyarticular course JIA		
5 In pJIA patients who failed MTX in recommended doses for at least 3 months, unless contraindicated, or toxicity/ intolerance occurs, a bDMARD should be considered. A bDMARD can be initiated earlier or in patients with few active joints taking into account prognostic factors and the pediatric rheumatologist opinion	1b; 3	9.2 (0.9)
6 TNFi, tocilizumab and abatacept are recommended for pJIA patients with inadequate response to csDMARDs. Rituximab may be considered in case of inadequate response to the previous bDMARDs	1b; 2b	9.4 (0.9)

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TABLE I. CONTINUATION

General principles	Level evidence	Agreement Mean(SD)
7 Assessment of response and the decision to maintain treatment should be performed no longer than 3 months after starting a bDMARD and biologic treatment should only be maintained in patients who achieve at least an ACRPed 50 or JADAS response	1b; 5	8.9 (1.1)
Biological therapy for systemic course JIA		
8 Systemic JIA is eligible for treatment with biologics if sustained severe systemic features persist regardless of concurrent therapy. Steroid dependence also constitutes an indication for bDMARD	1b; 5	9.6 (0.7)
9 IL-1 inhibitors (anakinra or canakinumab) or tocilizumab are recommended for refractory and/or steroid dependent sJIA	1b	9.3 (0.6)
10 Assessment of response and the decision to maintain treatment should be performed no longer than 1 month after starting a biologic in sJIA. Biologic treatment should only be maintained in patients who are free of systemic manifestations	1b; 5	8.6 (1.3)
Biological therapy for enthesitis-related arthritis		
11 Biological therapy should be considered in active polyarthritis and/or active enthesitis ERA patients with inadequate response to NSAIDs, at least one csDMARD, including MTX, and glucocorticoid injections, if appropriate	1b	9.2 (1.0)
12 TNFi are recommended for refractory ERA	1b	9.6 (0.2)
13 Assessment of response and the decision to maintain bDMARD should be performed no longer than 3 months after starting treatment in ERA patients. Biologic treatment should only be maintained in patients who achieve at least an ACRPed 50 and have documented improvement of enthesitis	1b; 5	8.9 (1.1)
Biological therapy for juvenile psoriatic arthritis		
14 Biological therapy should be considered in jPsA patients who failed at least one csDMARD, including MTX in recommended doses for at least 3 months, unless contraindication, toxicity or intolerance	1b	9.5 (0.7)
15 TNFi are recommended for refractory jPsA. Other biologics may be considered in case of inadequate response and/or major cutaneous involvement	1b	9.4 (0.8)
16 Assessment of response and the decision to maintain treatment should be performed no longer than 3 months after starting a biologic in jPsA patients. Biologic treatment should only be maintained in patients who achieve at least an ACRPed 50 and have documented improvement of extra-articular involvement (skin, dactilytis and enthesitis if applicable)	1b; 5	8.9 (0.9)
Tapering and stopping biological therapy		
17 Reducing and stopping biologic therapy might be attempted if sustained remission is achieved and maintained for more than 24 months	2b	9.1 (1.2)
Safety considerations		
18 All patients must be screened for tuberculosis, HIV, Hepatitis B and C virus infection prior to biological therapy	2b	9.9 (0.5)
19 Biological therapy should be discontinued prior to elective surgery and re-introduced only in the absence of infection and after satisfactory healing of surgical wound	4	9.7 (0.6)
20 Biological therapy should not be initiated in presence of active infection and must be discontinued until any serious infection is resolved	4	9.8 (0.5)

those with severe uveitis will develop visual impairment secondary to cataract, glaucoma, band keratopathy or macular pathology[10,11]. The prevention of irreversible damage and functional disability is the ultimate treatment goal, for which timely control of inflammation is indispensable[5]. Frequent assessment of disease activity is necessary in order to implement a treat-to-target strategy, aiming to achieve and maintain tight control, with treatment escalation if a target is not reached or if the disease relapses[12]. Early efficacious therapy results in clinical inactive disease in a larger number of patients, even with severe JIA[13]. Clinical evaluation of JIA patients should include the assessment of articular and extra-articular disease activity[1], as well as the evaluation of function and quality of life at regular time points. In order to standardize procedures across different pediatric rheumatology clinics, the monitoring of JIA should be done according to the Rheumatic Diseases Portuguese Register (Reuma.pt)/ /JIA protocol[16].

3. A definitive diagnosis of JIA and sustained articular, systemic or ocular inflammation are required when starting a biologic

A rheumatologist or a pediatrician with expertise in rheumatic diseases of childhood must establish a definitive diagnosis of JIA before starting biological therapy. JIA patients are eligible for biological therapy when active disease, defined as articular, systemic or ocular inflammation, persists despite appropriate conventional treatment as outlined in Figure 1, or when unacceptable side effects related to these medications are present. Children starting biologics should be registered and longitudinally followed-up in Reuma.pt.

4. The biologic choice must take into account the JIA phenotype

There are currently six biologics, with different modes of action, approved for use in JIA patients (Table III): three tumor necrosis factor (TNF) inhibitors (adalimumab, etanercept and golimumab), one interleukin (IL)-1 inhibitor (canakinumab), one IL-6 inhibitor (tocilizumab) and one T-cell co-stimulation blocker (abatacept). Yet, off-label use of other biologic disease modifying anti rheumatic drugs (bDMARDs) is frequent in clinical practice.

Tumor necrosis factor inhibitors (TNFi)

Etanercept is a fusion protein that had first proven efficacy in pJIA[17]. More recently, its efficacy was demonstrated in eoJIA (2-17 years), ERA and jPsA (12-17 years)[18]. Data from registries also documented its effectiveness with an encouraging safety profile[19]. Although the risk of severe adverse events seems higher with etanercept compared to MTX, the risk of malignancies was not significantly increased[20]. Patients on etanercept monotherapy developed more frequently incident inflammatory bowel disease and uveitis (0.5 and 0.8 events/100 years) than patients treated with etanercept in combination with MTX (0.1 and 0.2 events/100 years) or MTX alone (0.03 and 0.1

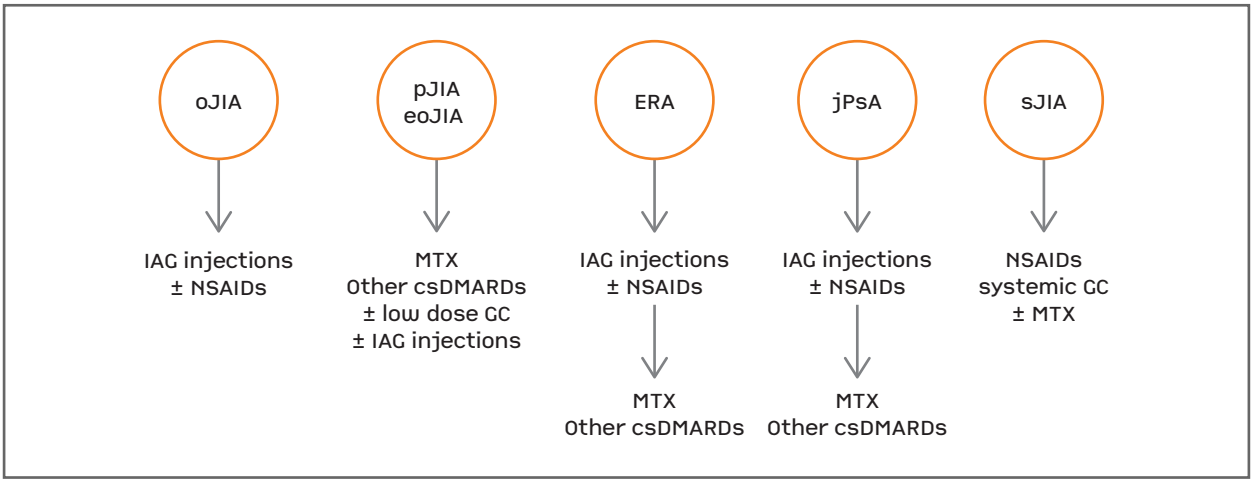

FIGURE 1. Conventional treatment according to JIA phenotype
Legend: JIA – Juvenile idiopathic arthritis; oJIA – oligoarticular JIA; pJIA – polyarticular JIA; eoJIA – extended oligoarticular JIA; ERA – enthesitis related arthritis; jPsA – juvenile psoriatic arthritis; sJIA – systemic JIA; IAG – intra-articular glucocorticoids; GC – glucocorticoids; NSAIDs – non-steroidal anti-inflammatory drugs; MTX – methotrexate

TABLE II. JADAS AND cJADAS CUT-OFF VALUES FOR oJIA AND pJIA DISEASE ACTIVITY STATES

	oJIA	pJIA
Disease activity states according to JADAS		
Inactive disease	≤1	≤1
Physician-assessed remission	≤2	≤2
Parent-assessed remission	≤2.3	≤2.3
Child-assessed remission	≤2.2	≤2.2
Minimal disease activity	≤2	≤3.8
Parent acceptable symptom state	≤3.2/3.5	≤5.2/5.4*
Child acceptable symptom state	≤3	≤4.3/4.5*
High disease activity**	>4.2	>8.5/10.5*
Disease activity states according to cJADAS* **		
Low disease activity	≤1.5	≤2.5
Moderate disease activity	1.51-4	2.51-8.5
High disease activity	>4	>8.5

Cut-off values apply to all versions of the Juvenile Arthritis Disease Activity Score (JADAS) versions, unless otherwise indicated.
*Cut-off value for JADAS27/cut-off value for JADAS10 and JADAS71.
**Cut-off values only apply to non-systemic JIA categories.
***Cut-off values for non-systemic JIA using the clinical Juvenile Arthritis Disease Activity Score (cJADAS)

events/100 years). Yet, the number of new events is very low[21,22]. A controlled pilot trial did not demonstrate superiority of etanercept over placebo in JIA associated uveitis[23] and a systematic review confirmed that etanercept is ineffective in chronic anterior uveitis[24]. Experience in treating patients below 2 years old is limited and the 13 patients from the BIKER register (4 sJIA, 4 eoJIA, 1 oJIA and 4 pJIA RF negative) constitute a valuable source of clinical experience[25]. At last observation, 6/11 patients reached ACRPed 70 response. The rate of adverse events (AE) in this age group is higher than previously described in older children[25,26]. Etanercept use in sJIA has been also reported and it is more efficacious in controlling arthritis than systemic features. Etanercept has been described either as treatment or as a trigger for the development of macrophage activation syndrome (MAS)[27-29]. A confounding by indication is plausible in this association.

Adalimumab is a fully human monoclonal antibody that binds to TNF. Recently, a multicenter open-label, phase 3b study in patients with active JIA, was conducted to assess the safety of adalimumab in patients with moderately to severely active pJIA, aged 2 to <4 years old or ≥4 years old weighting <15 kg[30]. At week 96, 92% of patients achieved ACRPed 30 and 77% achieved ACRPed 70. No new safety signals occurred, namely there were no opportunistic infections/tuberculosis, malignancies, or deaths reported. A multicenter, randomized placebo-controlled (RCT) parallel study in active and refractory juvenile onset ankylosing spondylitis (AS) documented higher response rates in the adalimumab group compared to placebo. At week 12 the BASDAI score decreased by 65%, back pain decreased by 50% and BASFI score by 47%, while CHAQ--DI score improved by 65%, all being statistically significant. There was no difference in the rate of AEs between groups. Injection site reactions were the most common AE[31]. Data from registries suggest adalimumab to be effective in the treatment of JIA associated uveitis, as well as in reducing the rate of uveitis flares[32,33]. A meta-analysis including 229 children with JIA associated uveitis has shown that adalimumab and infliximab have similar efficacy and are superior to etanercept. In the 40 months follow-up, uveitis more commonly remained in remission in those treated with adalimumab compared with infliximab (60% vs 18.8%)[34]. The results from a RCT to assess the efficacy of adalimumab in addition to MTX for the treatment of JIA associated uveitis are expected in the near future[35].

Infliximab is a chimeric monoclonal antibody not approved for JIA. A RCT showed improvement with infliximab in the majority of patients at 1 year, but did not meet its primary endpoint[36]. The clinical experience in JIA[37,38] and uveitis[39] demonstrates infliximab utility. Small observational studies in juvenile spondyloarthritis refractory to standard treatment documented good long-term control of axial disease, peripheral arthritis and enthesitis with infliximab[40,41].

Golimumab is a human monoclonal antibody binding both soluble and membrane bound forms of TNF recently approved for JIA. GO-KIDS, a three part withdrawal RCT, showed a 87% ACRPed 30 response rate during the open-label first 16 weeks on golimumab, but failed to meet its primary endpoint[42]. However, the Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a positive opinion, recommending the use of subcutaneous golimumab in combination with MTX for the treatment of pJIA in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with MTX[43]. In addition, case reports suggest that golimumab might be useful for the treatment of refractory JIA associated uveitis[44].

Certolizumab is a pegylated Fab'fragment of a hu-

manized TNF inhibitor antibody, not approved for JIA. The results of an open label phase 3 clinical trial in children with pJIA aged 2-17 years were not yet published[45].

Interleukin-1 inhibitors

Canakinumab is a monoclonal antibody that binds selectively to IL-1β. It was first approved for cryopirin-associated periodic syndromes and later for sJIA in children aged 2 years and older, with systemic features refractory to NSAIDs and glucocorticoids. It can be used alone or in combination with MTX. Data from a phase II dosage escalation open-label trial in 23 children receiving a single injection of canakinumab subcutaneously showed an immediate response, achieving at least an ACRPed 50 on day 15. Remission was observed in 18% of patients. Six of 11 non-responders to anakinra achieved at least an ACRPed 50 on day 15, after a single dose of canakinumab. AE were mild to moderate in severity and consisted mainly in infections and gastrointestinal symptoms. Three SAE occurred[46]. The evidence for approval was based on 2 RCTs[47]. In the placebo-controlled phase, there was a statistically significant relative risk reduction in time to flare of sJIA of 64% with canakinumab compared with placebo. Particular risks identified were serious infections, neutropenia, leukopenia and thrombocytopenia. In the pooled sJIA population, 85% of children and young people who received canakinumab experienced at least 1 adverse event. SAE were seen in 17% of this population.

Anakinra binds competitively to the IL-1 receptor, without inducing a stimulatory signal. A French retrospective study in 35 adults and children (20 with sJIA and 15 with adult-onset Still's disease) demonstrated improvement in 75% of sJIA patients[48]. All had refractory active arthritis and were previously treated with glucocorticoids, MTX, TNFi and/or thalidomide. Systemic symptoms remitted in 14 of 15 cases and the steroid dose was reduced in 50%. Two patients discontinued therapy because of severe skin reactions and another two due to infection. In 2011, a multicenter, randomized, double blind, placebo-controlled trial in 12 patients with sJIA showed an immediate and beneficial effect of anakinra on systemic features, as well as on joint inflammation[49]. No differences in AE were observed between groups. The efficacy of anakinra as a first-line disease-modifying therapy was also documented in sJIA, in some cases used as monotherapy[50]. Active arthritis resolved less frequently and less rapidly. Complete response was observed in 59% of the patients, while another 39% exhibited a partial response. Inactive disease was achieved in 80% patients on anakinra monotherapy. Although anakinra has very good results in the short term, these may not be sustained in the long term. Another caveat is the need for a daily injection, often associated with pain and injection site reactions. Furthermore, the risk of infections seems increased. Rare cases of MAS were described in patients taking anakinra. Conversely, there are MAS case reports successfully treated with anakinra[51,52]. As for etanercept confounding by indication might be related to the occurrence of this MAS cases.

IL-6 signaling inhibition

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that binds to membrane and soluble IL-6R, inhibiting IL-6–mediated signaling. It is approved for the treatment of sJIA and for the treatment of pJIA in children aged 2 years and older.

A phase 3 trial of TCZ in active sJIA patients, who were inadequate responders to NSAIDs and glucocorticoids, showed ACRPed 30, 70 and 90 responses of 85, 80 and 59%, respectively. During treatment, patients experienced significant catch-up growth, normalization of insulin-like growth factor 1 (IGF-1) levels, and bone balance favoring bone formation[53]. Of notice, there was also a beneficial effect in patients who had been previously treated with anakinra[54]. The extension phase demonstrated sustained effectiveness, good tolerability and a low discontinuation rate in the long-term treatment of children with sJIA. Safety issues include serious infections, neutropenia and increased liver enzymes[55]. A withdrawal RCT that enrolled 188 patients with pJIA (RF positive and RF negative) or eoJIA, who had failed or were intolerant to MTX, showed that 89% of patients achieved ACRPed 30, 62% ACRPed 70, and 26% ACRPed 90 response. Concurrent MTX decreased the risk of flare. The rate of AEs in the exposed population was 479.8 per 100 patient-years, most AEs were mild or moderate. The rate of serious infections (4.9/100 patient-year) was lower than the one reported for children with sJIA[56].

Tocilizumab has been used successfully in cases of uveitis associated with JIA unresponsive to prior TNF blockade[57,58] and in refractory idiopathic uveitis[59,60]. Based on anecdotal reports, tocilizumab might also be useful in the treatment of amyloidosis secondary to JIA[61,62].

Co-stimulatory blockade

Abatacept is approved for pJIA in combination with MTX, after failure of a TNFi. However, abatacept may

be an alternative to a TNFi, as first-line bDMARD, in particular circumstances. The first withdrawal RCT in children with JIA who failed previous treatments showed that abatacept decreased the number of arthritis flares[63]. Of TNFi naïve patients, 76% achieved ACRPed 30, 60% ACRPed 50, and 36% ACRPed 70 response, and 13% had inactive disease. Patients previously exposed to TNFi respond less frequently to abatacept (ACRPed 30/50/70 response in 39%/25%/ /11%, respectively). Improvements in health-related quality of life and sleep quality were also observed in the abatacept treated group[64]. Some recent data also suggest that abatacept might have a role in the treatment of refractory cases of JIA-associated uveitis[65,66].

B Cell depletion

Rituximab is not approved in JIAs, but based on several case series it can be an option, after failure of other biologics. An open label study including 55 children with severe pJIA or sJIA, documented a significant reduction of systemic manifestations and arthritis, with 52% of patients achieving remission by week 48[67]. Rituximab seems also to be effective for the treatment of refractory JIA associated uveitis[68]. It should be used with caution in children as long-lasting B-cell depletion is not uncommon following this therapy[69].

Possible future options

A long-term open-label study of *tofacitinib*, a JAK inhibitor that blocks signalling of multiple cytokines, is currently enrolling JIA patients to assess safety and tolerability in these patients[70]. *Ustekinumab*, an IL12/23 inhibitor, is effective in the treatment of psoriatic arthritis and psoriasis, inclusively in adolescents[71], yet not studied in JIA. Also, there is no reported experience with the IL-17 inhibitor *secukinumab* in children.

BIOLOGICAL THERAPY FOR POLYARTICULAR COURSE JIA

5. In pJIA patients who failed MTX in recommended doses for at least 3 months, unless contraindicated, or toxicity/intolerance occurs, a bDMARD should be considered. A bDMARD can be initiated earlier or in patients with few active joints taking into account prognostic factors and the pediatric rheumatologist opinion

A bDMARD should be started if there is an inadequate response after 3-6 months of treatment with conventional synthetic (cs)DMARDs, one of which must be MTX 15-20 mg/m^2/week for at least 3 months, unless contraindicated, or toxicity/intolerance occurs. Leflunomide can be an alternative in the absence of poor prognostic features[2][75]. However, for patients with poor prognostic factors an earlier start of a bDMARD may be appropriate (Figure 2), based on the concept of a window of opportunity[13,76]. The decision to initiate a bDMARD earlier or in patients with fewer active joints should be made on an individual basis taking into consideration prognostic features, functional impairment, drug side effects and the pediatric rheumatologist opinion.

6. TNFi, tocilizumab and abatacept are recommended for pJIA patients with inadequate response to csDMARDs. Rituximab may be considered in case of inadequate response to the previous bDMARDs

After failure of the maximum tolerated MTX dose or after failing a second csDMARD, if judged appropriate, TNFi or tocilizumab should be considered for active pJIA. Abatacept is indicated in pJIA patients unresponsive to TNFi. Rituximab should be reserved for refractory cases (Figure 2).

7. Assessment of response and the decision to maintain treatment should be performed no longer than 3 months after starting a bDMARD and biologic treatment should only be maintained in patients who achieve at least an ACRPed 50 or JADAS response

Since the development of preliminary definitions of improvement[77], the ACRPed response criteria have become the primary outcome measures in therapeutic trials in pJIA. The ACRPed includes PhGA measured in a 10 cm visual analogue scale (VAS), PGA measured in a 10 cm VAS, number of active joints, number of joints with limited motion, CHAQ and measurement of an acute phase reactant (CRP or ESR). This is a useful instrument for evaluating improvement following a given treatment, but the "core set" has not been validated for comparison between patients, and does not provide the level of disease activity. Instead, the composite score JADAS, can be used to assess treatment response on an individual level (Table II).

Maintenance of treatment requires that a meaningful clinical response is reached. The choice of a 3-month period is based on the time to achieve response observed in phase 3 trials with biologics in pJIA.

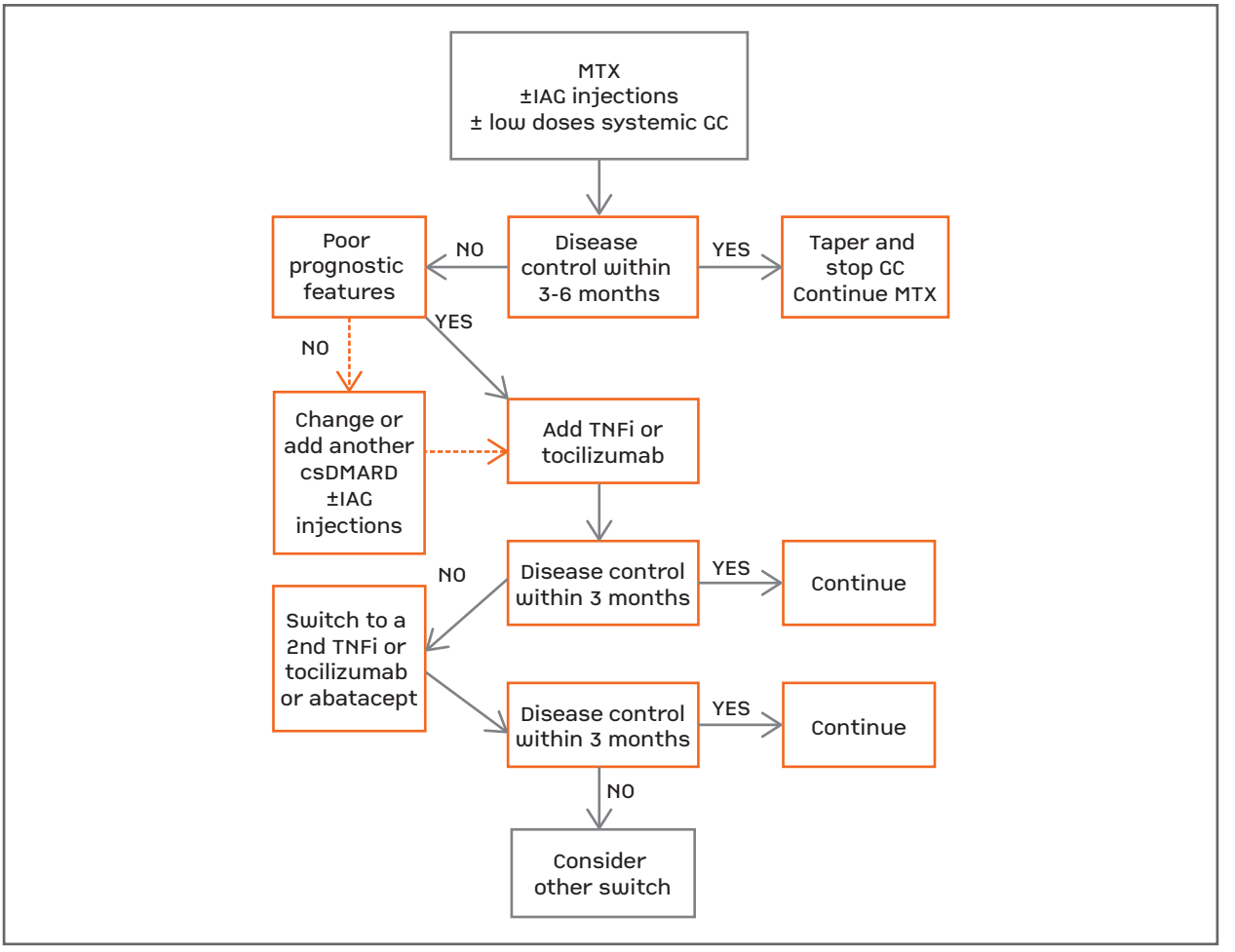

FIGURE 2. Polyarticular course JIA
Legend: JIA – Juvenile idiopathic arthritis; MTX-methotrexate; IAG – intra-articular glucocorticoids; GC – glucocorticoids; csDMARD – classic synthetic Disease Modifying Anti Rheumatic Drugs; TNFi – tumour necrosis factor inhibitor

ACRPed 50 response, defined as at least 50% improvement in 3/6 core response variables, with no more than 1 of the remaining measures worsening by >30%, must be reached in order to maintain biological therapy. Nevertheless, a higher response level should be aimed such as remission or a state of minimal clinical disease activity (MDA), defined as PhGA<=2.5 cm and swollen joint count of 0 in patients with oligoarthritis, or as PhGA<=3.4 cm, PGA<=2.1 cm, and swollen joint count <=1 in patients with polyarthritis[78]. Alternatively, JADAS improvement can be used, defined by a minimal decrease in the JADAS10 score according to baseline class: low by 4, moderate by 10 and high by 17[79].

If a patient fails the first biologic agent there is some evidence that a second biologic can be used with success[80].

BIOLOGICAL THERAPY FOR SYSTEMIC COURSE JUVENILE ARTHRITIS

8. Systemic JIA is eligible for treatment with biologics if sustained severe systemic features persist regardless of concurrent therapy. Steroid dependence also constitutes an indication for bDMARD

The initial treatment depends on the severity of clinical manifestations and usually includes NSAIDs and systemic glucocorticoids, as shown in Figure 3. Indications for glucocorticoids *ab initio* include symptomatic serositis, myocarditis, pleural effusions, pneumonitis, severe anemia and MAS. MTX should be started if active joints are present. Sustained severe systemic features that persist despite systemic glucocorticoids, with or without csDMARD, is an indication for starting

TABLE III. BIOLOGICS APPROVED FOR THE TREATMENT OF JIA PATIENTS

	Approved Indication	Age/body weight	Dosis
Abatacept	pJIA with inadequate response to TNFi. In combination with MTX	≥6 years	10 mg/kg 4/4 week, i.v.
Adalimumab	pJIA ERA	≥2 years ≥6 years	24 mg/m2 2/2 week s.c. (2-12 years)
Canakinumab	SJIA	≥2 anos	2 or 4 mg/Kg 4/4 week s.c.
Etanercept	pJIA ERA jPsA	≥2 years ≥12 years ≥12 years	0.8 mg/kg/week s.c.
Golimumab	pJIA in combination with MTX	≥ 40 Kg	50 mg once a month s.c.
Tocilizumab	sJIA pJIA	≥2 years	8 or 12 mg/Kg 2/2 week i.v. 8 or 10 mg/kg 4/4 week s.c.

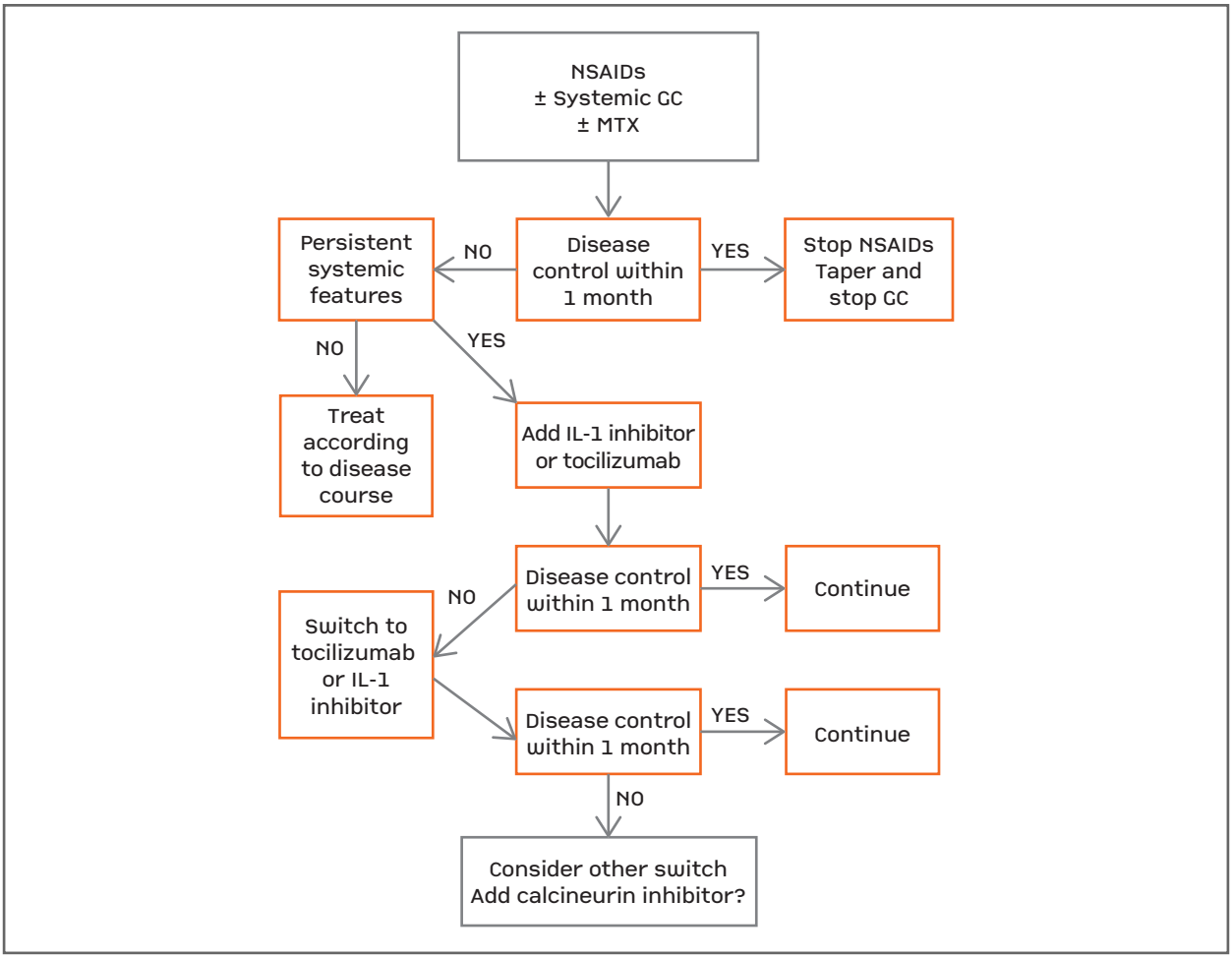

FIGURE 3. Systemic JIA with active systemic features
Legend: JIA – Juvenile idiopathic arthritis; MTX-methotrexate; GC – glucocorticoids; NSAIDs – non steroidal anti inflammatory drugs

a biologic. Besides, when JIA control is dependent on moderate/high doses of systemic glucocorticoids, starting a biologic is of utmost importance to prevent steroid induced irreversible side effects.

9. IL-1 inhibitors (anakinra or canakinumab) or tocilizumab are recommended for refractory and/or steroid dependent sJIA

IL-1 and IL-6 play a central role in the inflammatory process underlying sJIA and the inhibition of these cytokines has proved very effective in the control of systemic inflammation[47,81,82]. IL-1 inhibitors or tocilizumab can be used in addition to MTX or as monotherapy in refractory systemic JIA. There is good evidence of reduction and discontinuation of steroids in patients treated with these biologics[47,48,55].

10. Assessment of response and the decision to maintain treatment should be performed no longer than 1 month after starting a biologic in sJIA. Biologic treatment should only be maintained in patients who are free of systemic manifestations

IL-1 and IL-6 inhibitors provide prompt clinical response and normalization of acute phase reactants within the first days or weeks of treatment. In a multicenter trial involving 24 patients, fever and rash resolved very rapidly in >95% of patients and C-reactive protein (CRP) and ferritin normalized within 1 month in >80% of the patients after starting anakinra[49]. Approximately 60% of sJIA patients achieved ACRped 50 response 15 days after the first injection of canakinumab[46]. Acute phase reactants and fever rapidly normalized 2 weeks after the first infusion of tocilizumab and 52% of patients were able to discontinue oral glucocorticoids[54].

In case of persistent systemic manifestations, bDMARD must either be switched or the dose adjusted.

BIOLOGICAL THERAPY FOR ENTHESITIS-RELATED ARTHRITIS

11. Biological therapy should be considered in active polyarthritis and/or active enthesitis ERA patients with inadequate response to NSAIDs, at least one csDMARD, including MTX, and glucocorticoid injections, if appropriate

Initiation of a biologic is suitable for patients who have failed MTX in a dose of 15-20 mg/m^2/week for at least 3 months. Sulfasalazine can also be attempted before biological therapy. A few controlled trials showed its efficacy in a daily dose of 40-60 mg/kg/day, particularly in ERA and in arthritis associated with inflammatory bowel disease, with acceptable short-term safety profiles[83-85]. Intra articular glucocorticoid (IAG) injections should be considered. Initiation of a biologic is also recommended for patients who maintain active axial disease despite having failed two consecutive NSAIDs, at maximum recommended doses, for 1-3 months (Figure 4).

12. TNFi are recommended for refractory ERA

Both adalimumab and etanercept demonstrated superiority compared to placebo in the treatment of refractory ERA in double blind RCTs. The main outcomes included ACRPed 30, 50, 70 and 90, the number of tender joints, swollen joints and the number of tender enthesis sites[86,87]. Moreover, TNF blockade is particularly useful when there is axial disease[31]. In observational studies, anti-TNF treatment in ERA refractory to standard treatment results in good disease control. Outcomes included joint and enthesitis counts, as well as axial disease assessment using BASDAI and BASFI[41].

13. Assessment of response and the decision to maintain bDMARD should be performed no longer than 3 months after starting treatment in ERA patients. Biologic treatment should only be maintained in patients who achieve at least an ACRPed 50 and have documented improvement of enthesitis

Maintenance of treatment requires that a meaningful clinical response is reached. ACRPed 50 response and reduction of the number of painful enthesis sites by 50% must be obtained in order to maintain ongoing biological therapy. Although axial disease is uncommon in young children, it can occur as part of the spectrum of juvenile spondyloathritis[88]. A major clinical response, defined as a 50% improvement or more of the initial BASDAI, should be achieved in patients with predominantly axial involvement. The reason to choose a 3-month period is based on the time to achieve response observed in phase 3 trials with biologics in ERA.

BIOLOGICAL THERAPY FOR JUVENILE PSORIATIC ARTHRITIS

14. Biological therapy should be considered in jPsA patients who failed at least one csDMARD, including MTX in recommended doses for at least 3 months, unless contraindication, toxicity or intolerance

The treatment algorithm for jPsA is similar to that em-

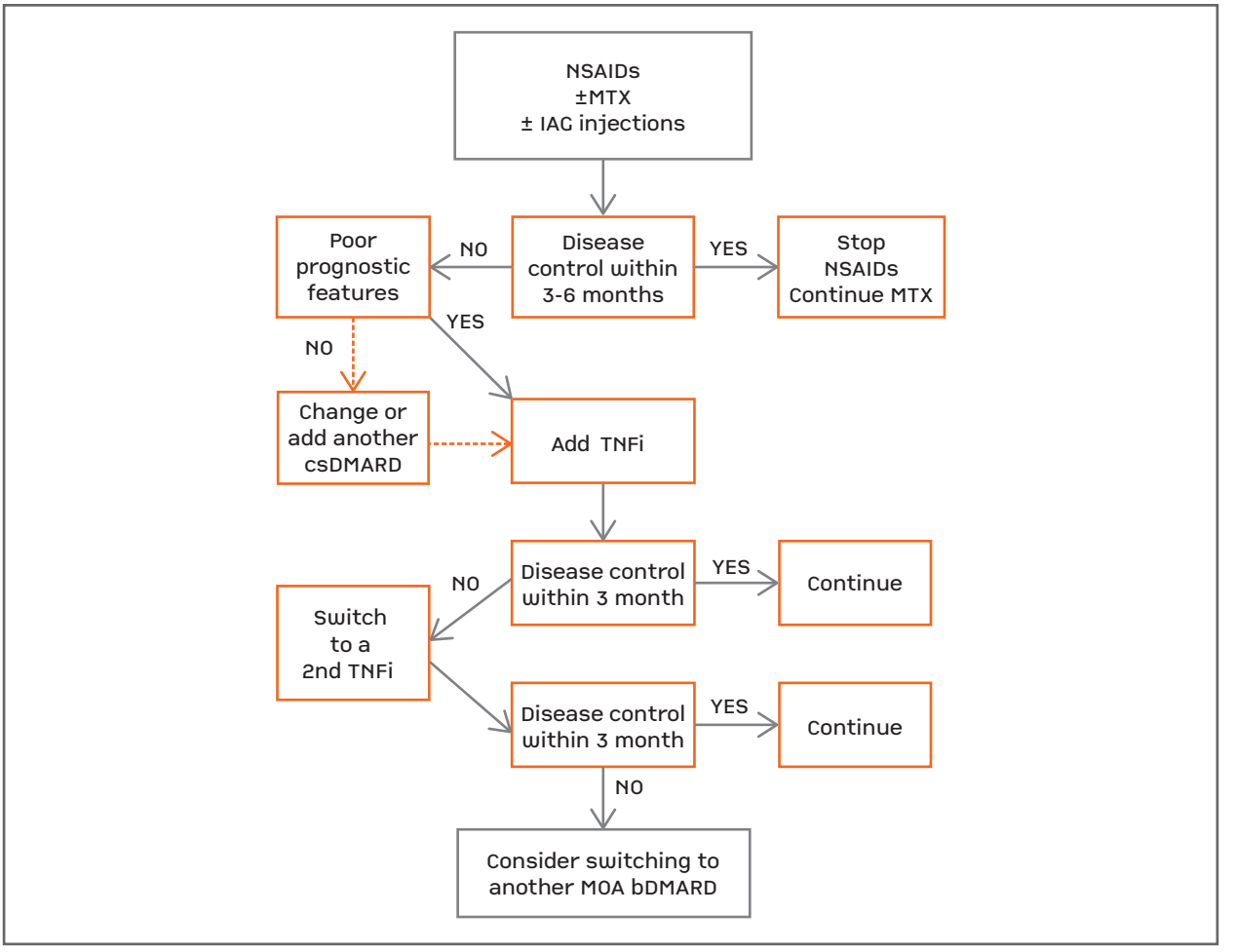

FIGURE 4. Enthesitis-related arhtritis
Legend: NSAIDs – non steroidal anti inflammatory drugs; MTX-methotrexate; GC – glucocorticoids; csDMARDs – classic synthetic Disease Modifying Anti Rheumatic Drugs; TNFi – Tumour Necrosis Factor inhibitor; bDMARD – biologic Disease Modifying Anti Rheumatic Drug; MOA – mode of action

ployed in other JIA categories, although the evidence for conventional treatment is mostly from adult PsA. NSAIDs are often employed initially and individual large joints can be treated effectively with IAG injections. In adult PsA patients MTX is effective for peripheral arthritis, with significant improvements in joint counts, pain and ESR[87]. Other csDMARD such as sulfasalazine, leflunomide and cyclosporine have demonstrated modest benefits[89]. Sulfasalazine is rarely prescribed for children younger than 2 years, due to paucity of safety data in this group[90]. Although axial disease is relatively common in older children it tends to run a milder course. Pharmacological treatment should be considered in patients who experience axial symptoms or show progressive limitation of spinal mobility. Anti-TNF therapy is highly effective in adult PsA patients with inadequate response to NSAIDs, as assessed both by symptoms and by MRI evidence of inflammation[91].

15. TNFi are recommended for refractory jPsA. Other biologics may be considered in case of inadequate response and/or major cutaneous involvement

Etanercept and adalimumab have been used successfully in jPsA and juvenile spondyloarthritis patients refractory to conventional treatment[18,40,92]. However, for skin involvement, it seems that the efficacy of etanercept on psoriasis and psoriatic nail disease may be lower or, at least, of slower onset, than for the antibodies

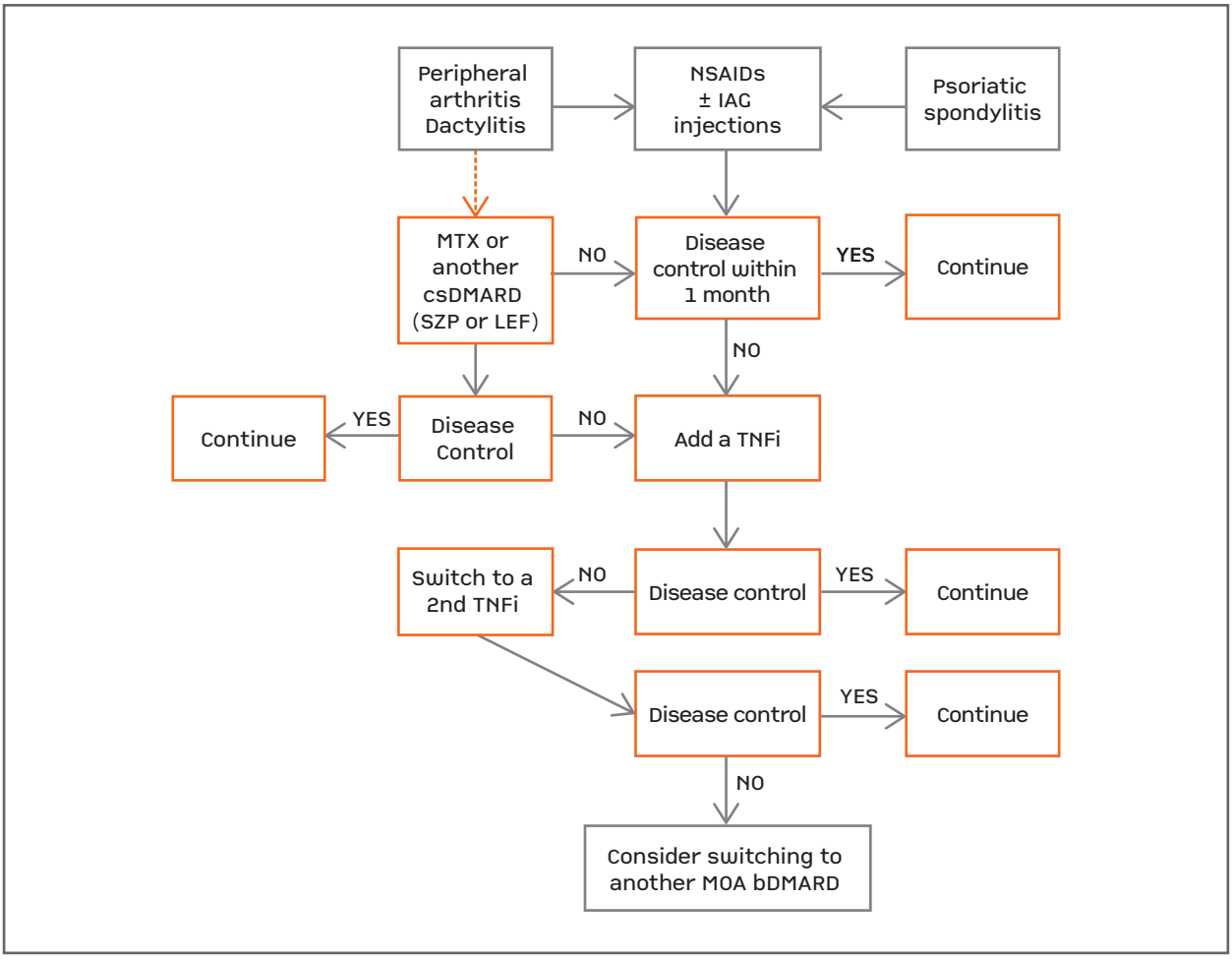

FIGURE 5. Juvenile Psoriatic Arhtritis
Legend: NSAIDs – non steroidal anti inflammatory drugs; MTX-methotrexate; GC – glucocorticoids; csDMARDs – classic synthetic Disease Modifying Anti Rheumatic Drug; SZP – Sulfasalazine; LEF – leflunomide; TNFi – Tumour Necrosis Factor inhibitor; MOA – mode of action

targeting TNF[93]. Other biological agents have been assessed in PsA but there is scarce data to ascertain efficacy and safety profile for their use in children[56,69,94]. However, ustekinumab, a monoclonal antibody against IL-12/23, is already approved for adults with PsA and for psoriasis in adults and children over 12 years and is a promising biological agent for jPsA with concomitant moderate–severe psoriasis[95]. Although switch has not been formally studied in jPsA, based in studies from adults, patients resistant to treatment can be switched to a second TNFi or to a bDMARD with a different mode of action.

16. Assessment of response and the decision to maintain treatment should be performed no longer than 3 months after starting a biologic in jPsA patients. Biologic treatment should only be maintained in patients who achieve at least an ACRPed 50 and have documented improvement of extra-articular involvement (skin, dactylitis and enthesitis, if applicable)

TNF inhibitors have demonstrated efficacy in jPsA, both for skin, nail, joint involvement, dactylitis and enthesitis[96]. ACRPed 50 response, reduction of the entheseal count and the number of digits involved by 50% should be achieved in order to maintain biological therapy. The reason to choose a 3-month period is based on the time to achieve response observed in phase 3 trials with biologics in jPsA.

TAPERING AND STOPPING BIOLOGICAL THERAPY

17. Reducing and stopping biologic therapy might be attempted if sustained remission is achieved and maintained for more than 24 months

The paramount goal of JIAs treatment is to achieve inactive disease and remission, with or without medication. Inactive disease is defined as no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis as defined by the SUN Working Group; ESR or CRP level within normal limits or, if elevated, not attributable to JIA; PhGA indicating no active disease (i.e. best score attainable on the scale used) and duration of morning stiffness of <15 minutes[97]. Inactive disease can also be defined for oJIA or pJIA using JADAS cut-off scores[15].

Six continuous months of inactive disease on medication defines clinical remission on medication, while 12 months of inactive disease off all anti-arthritis (and anti-uveitis) medications defines clinical remission off medication[98]. There is some evidence that at least one--third of patients can successfully undergo withdrawal of TNFi treatment for at least 12 months, but further studies are needed to accurately identify these patients[99]. It is unclear which approach is more advantageous, if to stop treatment abruptly or to taper it gradually.

SAFETY CONSIDERATIONS

Before starting and while on biologics, safety procedures and specific contraindications must be respected.

18. All patients must be screened for tuberculosis, human immunodeficiency virus, hepatitis B and C virus infection prior to biological therapy

The risk of developing tuberculosis (TB) is high among individuals treated with bDMARDs. With regard to TNFi the relative risk in adults is increased from 1.6 up to more than 25 times, depending on the clinical setting and the TNFi used, being higher for monoclonal antibodies[100-102]. Nevertheless, the existing data support a lower risk of developing TB among children who receive TNF antagonist therapies in industrialized countries, probably as a consequence of the lower prevalence of latent infection with *Mycobacterium tuberculosis* in children as compared to adults[103,104] (See Annexe I for screening and prophylaxis details).

Children with JIAs may be accidentally found to suffer from human immunodeficiency virus (HIV) infection or chronic hepatitis B or C. The presence of such an underlying chronic infection generates a number of practical issues regarding management of their arthritis with csDMARDs and bDMARDs[105] (See Annexe I for risk and screening details).

19. Biological therapy should be discontinued prior to elective surgery and re-introduced only in the absence of infection, and after satisfactory healing of surgical wound

A temporary suspension of the biological agent before elective surgery is recommended in order to reduce the risk of postoperative infection[106]. The half-live of the drug should be taken into account when planning presurgical interruption (Table IV). Almost complete elimination of the drug occurs after 5 half-lives. The type of surgery and the risk of infection based on the surgical procedure, as well as the general health of the patient and co-medication must be also considered. In case of an urgent surgery, biologic treatment should be temporarily withdrawn and the use of prophylactic antibiotics considered. Biologics can be restarted after satisfactory healing of the surgical wound, and signs of infection are excluded.

20. Biological therapy should not be initiated in presence of active infection and must be discontinued until any serious infection is resolved

The use of biological agents in patients with history of chronic or recurrent infections, or with conditions that predispose to infection, must be cautious. Patients who

TABLE IV. DISCONTINUATION OF BIOLOGICAL THERAPY BEFORE AN ELECTIVE SURGERY

Biologic	Half-live	Suspension before surgery
Abatacept	13 (8-25) days	8 weeks
Adalimumab	10-14 days	4 weeks
Anakinra	4-6 hours	24-48 hours
Canakinumab	23-26 days	8 weeks
Certolizumab	14 days	4 weeks
Etanercept	3-4 days	2 weeks
Golimumab	12 (7-20) days	8 weeks
Infliximab	8-10 days	4 weeks
Rituximab	32 (14-62) days	24 weeks
Tocilizumab	8-14 days	4 weeks

TABLE V. CONTRAINDICATIONS FOR BIOLOGICAL THERAPY

Absolute contraindications	Relative/temporary contraindications
Active infection, including tuberculosis and HBV+	Sexually active female without an effective contraception
Serious and/or recurrent infections	Known or predicted pregnancy
Recent history (<5 years) of malignancy	Breastfeeding
Demyelinating disease or optic neuritis*	Acute infection
Cardiac insufficiency class III/IV*	HCV infection
Known hypersensitivity to the active substance or excipients	HIV infection
Concomitant use of two or more biologics	Live attenuated vaccines in the last month
	Scheduled major surgery
	Active liver disease/hepatic impairment with AST or ALT>5x upper normal range

HBV – hepatitis B virus; HCV – hepatitis C virus; HIV – human immunodeficiency virus; AST – aspartate transaminase; ALT – alanine transaminase.
*Contraindication for TNFi

develop an infection during biological treatment must be carefully evaluated (search for constitutional symptoms, order complete blood count, CRP, bacteriological tests and appropriate imaging studies) and the administration of the biologic must be postponed until the infectious episode is controlled. In case of serious bacterial infection (*eg:* bacteraemia/sepsis, abscess/cutaneous ulcer, pneumonia, cellulitis, disseminated impetigo, bacterial endocarditis, acute pyelonephritis, intra-abdominal infection, osteomyelitis, septic arthritis, peritonitis, acute sinusitis with fever) or potentially serious or complicated viral infection (eg: EBV, CMV, parvovirus, varicella) consider also temporary withdrawal of the biologic.

CONTRAINDICATIONS

Absolute and relative contraindications, as well as reasons for temporary interruption of biologics are listed in Table V.

CONCLUSIONS

Biological therapy represents an advance in the treatment of JIA. The benefits and risks of these agents are known mainly from RCTs, but registries add relevant information to that knowledge. Precautions related to adverse events associated with the use of biologicals, namely infections, injection site reactions and potential risks associated to live vaccines should be taken into account when these drugs are prescribed.

1. Tools for assessing disease activity:

Joint disease - 1) Active joint count (presence of swelling not due to deformity, or limitation of motion with pain, tenderness or both) and/or 2) Juvenile Arthritis Disease Activity Score (JADAS), a composite index that uses the arithmetic sum of the active joint count assessed in 71 (JADAS71), 27 (JADAS27), or 10 (JADAS10) joints, physician global assessment (PhGA) of disease activity, parent/patient global assessment (PGA) of well-being and erythrocyte sedimentation rate (ESR) normalized to a 0–10 scale[14]. Clinical JADAS (cJADAS), without laboratory measures, is an alternative with good correlation with JADAS-ESR. JADAS cutoff values identifying different states of JIA activity for oligo and polyarthritis are shown in Table II[15]. Specific cut-off values for sJIA, ERA or jPsA have not yet been established.

Enthesitis - Entheseal count is suitable for documenting enthesitis activity.

Systemic features: Systemic symptoms (fever, rash, splenomegaly, lymphadenopathy) and inflammatory markers (raised ESR and C-reactive protein) were found to be the most important domains to evaluate systemic features

2. Prognostic factors

Children with persistent oJIA have a substantially better outcome than those with either sJIA or pJIA with regard to remission, disability and structural damage[72]. Diagnostic delay, greater severity and extension of

arthritis at onset, symmetric disease, early hip or wrist involvement, involvement of cervical spine, the presence of RF and/or anti-cyclic citrullinated peptide antibodies, early age at onset, female gender, family history of rheumatic disease and prolonged active disease are predictors of poor outcome[73, 74].

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ANNEXE I

SCREENING FOR CHRONIC INFECTIONS BEFORE STARTING A BIOLOGIC IN CHILDREN AND ADOLESCENTS WITH JIA

Tuberculosis

Screening for latent tuberculosis infection (LTBI) or active TB includes:

1. Full clinical history and physical examination comprising ethnicity, place of birth, history of recent exposure to TB, previous TB and its treatment, travel to endemic areas, any additional risk factors.
2. Chest radiography (findings suggestive of previous or active TB)
3. Tuberculin Skin Test (TST) should be performed before initiating any immunosuppressive treatment and repeated at screening prior to biological therapy. TST is considered positive in immunocompetent, BCG-vaccinated children if > 10 mm; and in children on immunosuppressive treatment or non-vaccinated children <= 5 years old if > 5 mm induration, taking epidemiological risk factors into account.
4. Interferon-γ release assay (IGRA)

Four meta-analyses of pediatric IGRA studies concluded that IGRAs have higher specificity for TB infection than the TST, particularly in settings of low TB burden and among BCG-vaccinated children. One meta-analysis estimated pooled specificities of 100%, 90%, and 56% for QFT, T-SPOT, and TST, respectively. IGRAs do not offer greater sensitivity than the TST. Sensitivity for both tests range between 62% and 90% for children with culture--confirmed TB disease. Furthermore, like the TST, IGRAs have poor sensitivity among immunocompromised patients and cannot differentiate LTBI from disease. Some studies show a better sensitivity for T-SPOT than QFT in immunocompromised patients. Of note, a lack of data on IGRA performance in children aged 0 to 4 years has led to hesitancy to use these assays in this age group.

5. The child should be referred to a Paediatrician or Paediatric Infectious Disease specialist or Paediatrics Pulmonologist with expertise in TB diagnosis and treatment if any of the screening procedures is positive, age < 5 years old or in case of doubt.
6. Preventive chemotherapy against TB is indicated in all patients with evidence of LTBI

   When TST and IGRA tests gave discordant results, the result of IGRA should prevail over TST in BCG-vaccinated children, especially if age ≥ 5 years. On the other hand, in non-vaccinated children a positive test result

(either TST or IGRA) should qualify for the individual to undergo preventive therapy. In this case of LTBI diagnosis, biological therapy should be postponed for 4 weeks after MT therapy is started. In patients with active tuberculosis biological therapy should be initiated after a full course of TB treatment has been completed. If JIA activity is very high an earlier initiation of biological treatment can be considered but never before the end of the first 2 months of TB treatment.

Patients should be carefully monitored for TB symptoms throughout the period they receive treatment with biological agents and for six months after discontinuation. Repeated testing for latent MT infection (every year) may be considered, especially in patients treated with anti-TNF monoclonal antibodies. However, repeated TST should be avoided as results might be distorted by boosting.

Fungal Infections

Unlike screening for TB, there are no guidelines on screening for fungal infections, such as *Histoplasma capsulatum* and *Coccidioides immitis*, which both have latent infections similar to TB, and so in endemic areas, serological screening should be performed before initiating a biologic. Furthermore, Listeria monocytogenes is an intracellular pathogen acquired via the ingestion of contaminated meats and dairy products. Newly acquired (and fatal) cases of listeriosis have occurred in patients who were taking TNFi. Patients should avoid unpasteurized dairy products while on biologic agents.

Hepatitis B virus infection

All patients starting DMARDs (biological or non-biological) should be screened for HBV infection with HBsAg, anti-HBc and anti-HBs.

1. An hepatologist should be consulted if JIA patients are found to have current or past HBV infection
2. Antiviral therapy should be initiated before DMARD therapy in patients with chronic HBV infection (HBsAg+)
3. Patients with past HBV infection (HBsAg–/anti-HBc+) do not need prophylactic antiviral treatment. However, increased vigilance for HBV reactivation is needed (frequent measurement of AST/ALT, HBV DNA levels).
4. If HBV DNA is found to be positive, initiation of antiviral therapy with the newer agents is recommended.

Hepatitis C virus infection

1. HCV screening is recommended before leflunomide and methotrexate use in the presence of hepatitis risk factors, and for all patients starting biologics
2. If HCV screening is positive the result should be confirmed by HCV RNA testing.
3. For patients found to have chronic HCV infection, referral to an hepatologist is recommended. Treatment decision should take into account several factors, for example the severity of liver disease, the likelihood of response to therapy (genotype-1 vs non-1), the likelihood of antiviral therapy-induced side effects (exacerbation of arthritis, psoriasis etc.), the presence of co-morbid conditions (cytopenias, renal dysfunction, mood disorders, etc.) and patient/parents willingness.
4. In general, methotrexate and leflunomide are contraindicated in HCV-infected patients, although data regarding their safety for patients with mild or moderate liver fibrosis are not available.
5. Biological agents can be used in patients with non-advanced liver disease (Child–Pugh class A).
6. In the most recent ACR recommendations, etanercept was suggested as the preferred agent for patients with RA and chronic hepatitis C (level of evidence C). Monotherapy with rituximab is also a potential agent to use for such patients.

Human immunodeficiency virus infection

1. Patients should be screened for HIV infection before starting a biologic agent. If positive an expert in pediatric HIV infection should be consulted.
2. TNFi therapy is a viable alternative for refractory JIA patients with HIV infection, without advanced disease.